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Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Exhibit A

(54) Title: COMPOSITIONS AND METHODS FOR DIAGNOSTICS AND THERAPEUTICS FOR HYDROCEPHALUS

(57) Abstract: The present disclosure relates to RFX4_v3 protein and nucleic acids encoding RFX4_v3 protein. The present disclosure provides non-human transgenic animals with altered RFX4_v3 genes, and provides assays for the detection of RFX4_v3 and RFX4_v3 polymorphisms associated with disease states. The present disclosure additionally provides methods of determining a subjects' risk of developing congenital hydrocephalus, and treating or inhibiting its development.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/12348

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07K 1/00, 14/00, 17/00; A61K 39/00
US CL : 530/350; 424/185.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 530/350; 424/185.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	WO 02/086071 A2 (LUDWIG INSTITUTE FOR CANCER RESEARCH) 31 October 2002, see the entire document, particularly SEQ ID NO:8, page 3, lines 11-19, page 8, lines 3-7, page 34, lines 12-24, and example 5 on page 73.	1-2, 14, 22-23 and 47-48

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/12348

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2 ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-4,14,22-24,47 and 48

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-4, 14, 22-24 and 47-48, drawn to drawn to a substantially purified RFX4_v3 polypeptide and a method for generating antibodies specific for an RFX4_v3 polypeptide.

Group II, claims 4-13 and 25, drawn to an isolated nucleic acid molecule encoding RFX4_v3 polypeptide, a vector, a transformed host cell, and a method for producing a variant of a RFX4_v3 polypeptide by mutanizing the wild-type sequences.

Group III, claims 15-21, 26-35, 40-41 and 44-45, drawn to an isolated nucleic acid molecule that hybridizes under conditions of low stringency to the recited target nucleic acid molecule, a vector, a transformed host cell, a composition comprising the same, and a method for detecting a nucleic acid molecule in a biological sample using a hybridization technique and a method of identifying a subject at risk of developing RFX4_v3 linked hydrocephalus comprising detecting in the subject an abnormality in a RFX4_v3 nucleotide sequence that alters expression of the RFX4_v3, and a kit for determining if a subject is a carrier of a mutated RFX4_v3 gene.

Group IV, claims 31, 36-44, 46 and 49, drawn to an RFX4_v3 specific antibody, a kit for determining if a subject is a carrier of a mutated RFX4_v3 gene comprising the same.

Group V, claims 50-57, drawn to a transgenic mouse whose somatic and germ cells comprise a disrupted endogenous RFX4_v3 gene and a method for generating a non-human transgenic animal with a knockout for the RFX4_v3 gene.

Group VI, claim 58, drawn to a method for screening compounds for the ability to alter RFX4_v3 activity having the specific steps recited in claim 58.

Group VII, claims 59-62, drawn to a pharmaceutical composition for treating or preventing congenital hydrocephalus comprising a therapeutically effective amount of a RFX4_v3 polypeptide, variant or portion thereof and a method of treating congenital hydrocephalus in a subject using the same.

Group VIII, claims 59-61 and 63-64, drawn to a pharmaceutical composition for treating or preventing congenital hydrocephalus comprising a therapeutically effective amount of a RFX4_v3 nucleic acid, variant or portion thereof and a method of treating congenital hydrocephalus in a subject using the same

The inventions listed as Groups 1-8 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The RFX4_v3 polypeptide of Group 1, the nucleic acid molecule encoding RFX4_v3 polypeptide of Group 2, the nucleic acid probe molecule of Group 3, the RFX4_v3 specific antibody of Group 5 and the non-human transgenic animal with a knockout for the RFX4_v3 gene of Group 6, the pharmaceutical compositions of Groups 7-8 are different chemically and physically as well as they have different properties. Therefore, they do not have the same special technical features. The methods of Groups 1-8 also do not share the same special technical features because a step for each method would constitute a special technical feature for that method. For example, unlike methods of other Groups the method of Group 1 requires the step of injecting an animal with an RFX4_v3 polypeptide or an immunogenic portion thereof to generate antibodies. The method of Group 2 requires the stesp of mutanizing the wild type nucleic acid sequences and screening the variants for RFX4_v3 activity. The method of Group 3 requires the step of detecting a RFX4_v3 nucleic acid molecule or an abnormality in the nucleic acid molecule in a biological sample, whereas the method of Group 4 requires the step of detecting an abnormality in a RFX4_v3 polypeptide. The method of Group 5 requires the necessary step of disrupting an RFX4_v3 transcript in a non-human transgenic animal with the methods of Groups 7-8 are directed to treatment methods of congenital hydrocephalus using protein therapy and gene therapy approach, respectively. The screening method of Group 6 requires the specific recited steps that are not needed in any other methods.

Continuation of B. FIELDS SEARCHED Item 3:
APS, DIALOG, MEDLINE, EMBASE, BIOSIS
search terms: RFX4, v3, variant, SEQ ID NOs: 8, 6 and 10.